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Comment on "Conformational analysis of small organic molecules using NOE and RDC data: A discussion of strychnine and α-methylene-γ-butyrolactone"

In a recent paper published in this journal, Kolmer et al. [1] reported an experimental approach for conformational analysis of small organic molecules using NOE and RDC techniques. The authors obtained information on conformation of strychnine and α-methylene-γ-butyrolactone molecules. In addition, possible sources of error in the measurement and analysis process and ideas of how to exclude them were discussed.

While the conclusion that different NMR techniques, NOE and RDC sometimes predict the same results is entirely uncontroversial, Kolmer et al. have misrepresented and misquoted Tropp's work [2] to an extent that we feel impelled to make a number of clarifications. Hereafter, we use the notation of and references to the equations of Ref. [1].

Averaged interproton distances are not defined correctly by the formula (2) on page 102 [1]:

$$r_{IS,averaged,Tropp} = \left(\sum_{\mu=1}^{N} p_\mu r_{IS,\mu}^{-3}\right)^{-\frac{1}{3}}$$

where N is the number of conformers, p_μ is the population of the conformer μ, and $r_{IS,\mu}$ is the distance between the protons I and S in the conformer μ.

It is inconsistent with the physical meaning since the distance between particles experiencing dipole–dipole interaction cannot be a function of the energy in the power of −3; the power index of −6 should be used due to statistical averaging of the interaction caused by heat motion of the particles [3]. To our knowledge, use of this rough model for estimating conformer fractions of molecules in solution can lead to unpredictable errors.

Different averaging models for interatomic distances in small molecules were compared recently [4–6]; it was shown that each type of motion is better described by its own model. Thus, for average of distances involving atoms of a methyl group, the following formula is the best choice:

$$r_{eff} = \left[\frac{1}{5}\sum_{k=-2}^{2}\left|\frac{1}{3}\sum_{i=1}^{3}\frac{Y_{2k}(\theta_{mol}^{i}, \varphi_{mol}^{i})}{r_i^3}\right|^2\right]^{-1/6},$$

where $Y_{2k}(\theta_{mol}^{i}, \varphi_{mol}^{i})$ are the second rank spherical harmonics.

Based on the above discussion, we have here corrected a number of misrepresentations in the recent publication [1] and we draw attention to that interproton distances should be averaged using the Tropp's model which allows for angles and second rank spherical harmonics to describe rotation of methyl groups; not direct multiplication by the distance but the inverse correlation with the power index of −6 should be used in calculations of conformer fractions.

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References

[1] A. Kolmer, L.J. Edwards, I. Kuprov, C.M. Thiele, Conformational analysis of small organic molecules using NOE and RDC data: a discussion of strychnine and α-methylene-γ-butyrolactone, J. Magn. Reson. 261 (2015) 101–109, http://dx.doi.org/10.1016/j.jmr.2015.10.007.

[2] J. Tropp, Dipolar relaxation and nuclear Overhauser effects in nonrigid molecules: the effect of fluctuating internuclear distances, J. Chem. Phys. 72 (1980) 6035–6043, http://dx.doi.org/10.1063/1.439059.

[3] I.G. Kaplan, Intermolecular Interactions: Physical Picture, Computational Methods and Model Potentials, John Wiley & Sons, 2006, http://dx.doi.org/10.1002/047086334X.

[4] I.A. Khodov, S.V. Efimov, V.V. Klochkov, G.A. Alper, L.A.E. Batista de Carvalho, Determination of preferred conformations of ibuprofen in chloroform by 2D NOE spectroscopy, Eur. J. Pharm. Sci. 65C (2014) 65–73, http://dx.doi.org/10.1016/j.ejps.2014.08.005.

[5] I.A. Khodov, S.V. Efimov, V.V. Klochkov, L.A.E. Batista de Carvalho, M.G. Kiselev, The importance of suppressing spin diffusion effects in the accurate determination of the spatial structure of a flexible molecule by nuclear Overhauser effect spectroscopy, J. Mol. Struct. 1106 (2016) 373–381, http://dx.doi.org/10.1016/j.molstruc.2015.10.055.

[6] I.A. Khodov, S.V. Efimov, M.Y. Nikiforov, V.V. Klochkov, N. Georgi, Inversion of population distribution of felodipine conformations at increased concentration in dimethyl sulfoxide is a prerequisite to crystal nucleation, J. Pharm. Sci. 103 (2014) 392–394, http://dx.doi.org/10.1002/jps.23833.

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